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Erstveröffentlichung in / First published in:

Urologia Internationalis. 2017, 99 (2), S. 177 – 185 [Zugriff am: 19.05.2020]. Karger. ISSN 1423-0399.

DOI: <https://doi.org/10.1159/000477263>

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Evaluation of Prostate Imaging Reporting and Data System Classification in the Prediction of Tumor Aggressiveness in Targeted Magnetic Resonance Imaging/Ultrasound-Fusion Biopsy

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Keywords

Magnetic resonance imaging/ultrasound-fusion biopsy · Multiparametric MRI · Prostate Imaging Reporting and Data System · Prediction · Prostate cancer · Systematic biopsy

Abstract

Objectives: The study aimed to evaluate the prediction of Prostate Imaging Reporting and Data System (PI-RADS) with respect to the prostate cancer (PCa) detection rate and tumor aggressiveness in magnetic resonance imaging (MRI)/ultrasound-fusion-biopsy (fusPbx) and in systematic biopsy (sysPbx). **Materials and Methods:** Six hundred and twenty five patients undergoing multiparametric MRI were investigated. MRI findings were classified using PI-RADS v1 or v2. All patients underwent fusPbx combined with sysPbx (comPbx). The lesion with the highest PI-RADS was defined as maximum PI-RADS (maxPI-RADS). Gleason Score ≥ 7 (3 + 4) was defined as significant PCa. **Results:** The overall PCa detection rate was 51% ($n = 321$; 39% significant PCa). The detection

rate was 43% in fusPbx ($n = 267$; 34% significant PCa) and 36% in sysPbx ($n = 223$; 27% significant PCa). Nine percent-age of significant PCa were detected by sysPbx alone. A total of 1,162 lesions were investigated. The detection rate of significant PCa in lesions with PI-RADS 2, 3, 4, and 5 were 9% (18/206), 12% (56/450), 27% (98/358), and 61% (90/148) respectively. maxPI-RADS ≥ 4 was the strongest predictor for the detection of significant PCa in comPbx (OR 2.77; 95% CI 1.81–4.24; $p < 0.005$). **Conclusions:** maxPI-RADS is the strongest predictor for the detection of significant PCa in comPbx. Due to a high detection rate of additional significant PCa in sysPbx, fusPbx should still be combined with sysPbx.

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Introduction

Multiparametric magnetic resonance imaging (mpMRI) plays an increasingly important role in the diagnosis of prostate cancer (PCa). mpMRI detects clinically significant PCa with a relatively high sensitiv-

Table 1. Sequence parameters of multiparametric MRI protocol

Parameter	T1 TSE	T2 TSE	SS Epi DWI	Dynamic contrast-enhanced TWIST	T1 TSE with fat suppression
Plane	Axial	Axial, sagittal	Axial	Axial	Axial
RT/ET, ms	600/11	10,000/123	8,300/93	4.83/1.87	750/11
Field of view, mm	330 × 288	200 × 200	221 × 260	260 × 260	320 × 288
Matrix	320 × 288	320 × 320	160 × 136	192 × 192	320 × 288
Sections	39	26	26	–	39
Interslice gap, mm	–	–	0	–	–
b-value, s/mm ²	–	–	0; 500; 1,000; 1,500; 2,000	–	–
Section thickness, mm	5	3	3	3	5
Acquisition time, min	02:57	04:51	07:38	04:26	02:46

TSE, turbo spin echo; TWIST, time-resolved imaging with stochastic trajectories; DWI, diffusion-weighted imaging; RT, repetition time; ET, echo time.

ity and specificity [1, 2]. Improved visualization of cancer foci and targeting of tumor-suspicious lesions by MRI/ultrasound-fusion biopsy (fusPbx) leads to an increased detection of clinically significant PCa [3, 4]. This enables a more accurate risk-stratification and thus, a better counseling of patients for treatment strategies.

The Prostate Imaging Reporting and Data System (PI-RADS) was published in 2012 as a consensus-based guideline by the European Society of Urogenital Radiology (ESUR) to standardize the evaluation and reporting of prostate MRI [5]. Several studies revealed that PI-RADS appears to have a reliable diagnostic accuracy and correlation with tumor aggressiveness [6–8]. Furthermore, it shows a good inter-reader agreement [9]. Especially lesions classified as PI-RADS 4 and 5 harbor a high portion of high-grade PCa [7].

In 2014, the ESUR published an updated version of the PI-RADS classification system (PI-RADS v2). PI-RADS v2 intends to represent a guideline for minimally acceptable technical parameters of mpMRI. PI-RADS v2 aimed to simplify mpMRI reports and to reduce the inter-reader variability [10].

The aim of this study was to evaluate the prediction of PI-RADS with respect to the tumor-detection rate and tumor aggressiveness in targeted transperineal fusPbx as well as in combination of fusPbx and transrectal systematic biopsy (sysPbx). Furthermore, we assessed the value of PI-RADS 2 and 3 lesions for targeted biopsy and for combined biopsy (comPbx) with respect to the biopsy results.

Methods

Data were collected prospectively with the approval of the Institutional Review Board of the University of Dresden (Vote: EK53022014). This study included only those patients who had an mpMRI performed and evaluated according to the START criteria [11] and in whom PI-RADS could be applied.

Patients underwent mpMRI either at the Department of Radiology of our hospital or at ambulatory radiology offices. At the Department of Radiology of our hospital, mpMRIs were performed on a 3-tesla MR system (Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany). A 6-channel body matrix coil was used in combination with the system's integrated 12-channel spine matrix coil for signal acquisition. The mpMRI protocol is shown in Table 1. Dynamic contrast-enhanced, time-resolved imaging with stochastic trajectories was performed with 75 acquisitions. The acquisition of the dynamic contrast-enhanced images started simultaneously with the start of an intravenous injection of 20 mL 0.5 M gadopentate dimeglumine (Magnevist, Bayer Schering Pharma, Berlin, Germany) with an injection rate of 2 mL/s, followed by a 20 mL flush of 0.9% saline, also injected with 2 mL/s. The total MRI acquisition time was 25 min.

All MR images were evaluated prospectively by board-certified radiologists with more than 10 years of experience in prostate MRI. Based on the criteria of ESUR [5, 10], PI-RADS v1 or v2 was used to evaluate tumor-suspicious lesions. The mpMRI of patients examined before April 2015 was evaluated according to PI-RADS v1. If patients had an mpMRI done since April 2015, mpMRI was evaluated according to PI-RADS v2. A reevaluation according to PI-RADS v2 in mpMRIs evaluated by PI-RADS v1 and vice versa was not performed. Lesions classified according to PI-RADS v1 and v2 were defined as follows: PI-RADS 1: clinically significant PCa is highly unlikely; PI-RADS 2: clinically significant PCa is unlikely; PI-RADS 3: clinically significant PCa is equivocal; PI-RADS 4: clinically significant PCa is likely; PI-RADS 5: clinically significant PCa is highly likely.

The BioJet-System (D&K Technologies, Barum, Germany) was used for fusPbx. Targeted biopsy was performed in a transperineal approach while taking at least 2 cores per lesion. Lesions classified as PI-RADS ≥ 2 were biopsied. Subsequently, every patient underwent a transrectal sysPbx. sysPbx was performed according to an in-house scheme covering 12 regions of the prostate. sysPbx was completed by the same urologist who had performed the targeted biopsy.

All biopsy specimens were investigated at the Department of Pathology of our hospital by an experienced uropathologist. We defined a Gleason Score (GS) ≥ 7 (3 + 4) as significant PCa. The maximum PI-RADS (maxPI-RADS) in mpMRI was defined as the lesion with the highest PI-RADS of all lesions per patient. The influence of the maxPI-RADS for the biopsy results in comPbx was investigated. Furthermore, all lesions detected in mpMRI were evaluated based on the tumor-detection rate and GS. Lesions classified as PI-RADS 2 and PI-RADS 3 were evaluated for tumor detection when these lesions existed alone or beside other lesions classified with a higher PI-RADS.

Patient-based (maxPI-RADS) analysis and lesion-based (all lesions in mpMRI) analysis of detection rates in lesions detected in mpMRI were performed.

Data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Chi-square-test was used to determine differences between numerical and categorical variables. The McNemar test was employed to compare the detection rate of fusPbx to sysPbx. A p value < 0.05 was considered statistically significant. Logistic regression analysis was used to evaluate the prediction of maxPI-RADS. Receiver operating characteristics (ROC) analyses, calculating the area under the curve (AUC), were used to compare the ability to predict the detection of PCa.

Results

Seven hundred and seventy five patients were evaluated retrospectively. One hundred and thirty nine patients were excluded due to MRIs not fulfilling the START-criteria or due to incomplete imaging data set. In 114 of these patients, mpMRI were performed in ambulatory radiology offices. Eleven patients were excluded because of suspicion of PCa relapse after radiotherapy required additional biopsy or due to a performed transperineal sysPbx. Finally, further investigations were carried out on the remaining 625 patients. Patients' demographic details of the study cohort are depicted in Table 2.

The overall cancer-detection rate and detection rate of significant PCa defined as GS ≥ 7 (3 + 4) in comPbx, fusPbx, and sysPbx are shown in Table 3.

Overall ($n = 625$), 31% of PCa (98/321) were detected in fusPbx alone; 17% of PCa (54/321) were detected in sysPbx alone. fusPbx alone would have detected 28% of significant PCa (68/246). SysPbx alone would have detected 9% significant PCa (23/246). Missing rates of all

Table 2. Patients' demographics, findings in mpMRI, and histopathology of prostate biopsy cores

Parameter	Value
Age, years, median (min; max)	66 (46; 86)
PSA, ng/mL, median (min; max)	8.17 (1; 112)
Positive findings in DRE, n	83
First biopsy, n	133
Repeat biopsy, n	445
Patients with known PCa (under active surveillance), n	47
Prostate volume, mL, median (min; max)	50 (12; 270)
Overall biopsy cores per patient, n (median)	19 (11; 27)
Targeted biopsy cores per patient, n (median)	7 (2; 16)
Systematic biopsy cores per patient, n (median)	12 (8; 16)
Number of lesions/patient, mean \pm SD	1.9 \pm 0.9
<i>MRI before prostate biopsy</i>	
PI-RADS v1, n	458
PI-RADS v2, n	167
<i>mpMRI performed at</i>	
In-house radiology department, n	605
Ambulatory offices, n	20
Total number of lesions	1,162
PI-RADS of lesion, n	
2	206
3	450
4	358
5	148
maxPI-RADS in investigated patients, n	
2	65
3	196
4	247
5	117
Localization of positive lesions, n (%)	
Peripheral zone	262 (23)
Central zone	119 (45)
Ventral zone	72 (27)
Overlapping in different regions	68 (26)
	3 (1)
<i>Histological findings in combined prostate biopsy</i>	
Gleason Score of biopsy (combination of targeted and systematic biopsies), n	
No tumor	304
3 + 3 = 6	75
3 + 4 = 7	143
4 + 3 = 7	37
≥ 8	66

and significant PCa by fusPbx and sysPbx in patients undergoing first biopsy, repeat biopsy, or control biopsy for active surveillance protocols are presented in Table 4.

In patients on active surveillance undergoing control biopsy by comPbx, tumor upgrading to significant PCa occurred in 61% (22/36) of patients (in fusPbx: 74% [20/27]; in sysPbx: 54% [14/26]; $p = 0.109$).

Table 3. Detection of prostate cancer and detection rate of significant PCa defined as GS ≥ 7 (3 + 4) in the comPbx, fusPbx alone, and sysPbx alone

	Detection rate of all Pca				Detection rate of significant PCa			
	comPbx	fusPbx	sysPbx	p value (fusPbx vs. sysPbx) [†]	comPbx	fusPbx	sysPbx	p value (fusPbx vs. sysPbx) [†]
All patients (n = 625)	321 (51)	267 (43)	223 (36)	<0.005	246 (39)	213 (34)	167 (27)	<0.005
First biopsy (n = 133)	70 (53)	65 (49)	55 (41)	0.041	59 (44)	54 (41)	47 (35)	0.143
Repeat biopsy (n = 445)	215 (48)	175 (39)	142 (32)	0.002	165 (37)	139 (31)	106 (24)	<0.005
Active surveillance (n = 47)	36 (77)	27 (57)	26 (55)	1.0	22 (47)	20 (43)	14 (30)	0.109

The values are n (%).

[†] McNemar-test.

Table 4. Missed PCa in sysPbx and MRI/fusPbx

Indication of biopsy	sysPbx		fusPbx	
	missed PCa (all)	missed significant PCa	missed PCa (all)	missed significant PCa
All patients (n = 625)	98 (31)	68 (28)	54 (17)	23 (9)
First biopsy (n = 133)	15 (21)	9 (15)	5 (7)	3 (5)
Repeat biopsy (n = 445)	73 (34)	52 (32)	40 (19)	19 (12)
Control-biopsy for active surveillance protocol (n = 36)	10 (28)	7 (32)	9 (25)	1 (5)

Values are n (%).

*Comparison of mpMRI to the Biopsy Results:
A Lesion-Based Analysis*

Figure 1 represents the overall cancer-detection rate and the detected GS per lesion in all patients and in subgroups. Especially, patients with the first biopsy showed higher detection rates of significant PCa in lesions classified as PI-RADS 4 and 5. Overall, the detection of significant PCa was significantly higher in lesions classified as PI-RADS ≥ 4 compared to lesions classified as PI-RADS ≤ 3 (37% [188/506] vs. 11% [74/656], $p < 0.005$). In ROC-analysis, the AUC of PI-RADS was 0.726 (95% CI 0.690–0.762) for the detection of significant PCa (Fig. 2). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for the detection of significant PCa in lesions classified as PI-RADS ≥ 4 was 72, 65, 37, 89, and 66%, respectively.

Regarding only lesions classified as PI-RADS 2, 88% of these lesions (181/206) did not harbor PCa. Nine percent of PI-RADS 2 lesions showed evidence of significant PCa

(18/206; in 17 patients). In 3% (7/206) of PI-RADS 2 lesions, PCa of GS 6 was detected. Thirty-three percent of lesions harboring significant PCa (6/18) were associated with another lesion with proven significant PCa. All of these associated lesions were classified as PI-RADS ≥ 4 . In total, 65 patients (10%) presented only PI-RADS 2 lesions. Of these patients, 11 harbored significant PCa in these lesions. In 6 of these patients, significant PCa was detected in sysPbx as well, and 5 of them did not present significant PCa in sysPbx. However, 6 patients with only PI-RADS 2 lesions lacking evidence of significant PCa presented a significant PCa in sysPbx. In total, 7% of significant PCa (17/246) would not have been detected, if patients presenting exclusively PI-RADS 2 lesions would not have undergone either targeted or sysPbx.

Regarding PI-RADS 3 lesions, 80% of these lesions (362/450) did not harbor PCa. 12.4% PI-RADS 3 lesions (56/450; 34 patients) showed evidence of significant PCa. In 7% (32/450) of PI-RADS 3 lesions, PCa of GS 6

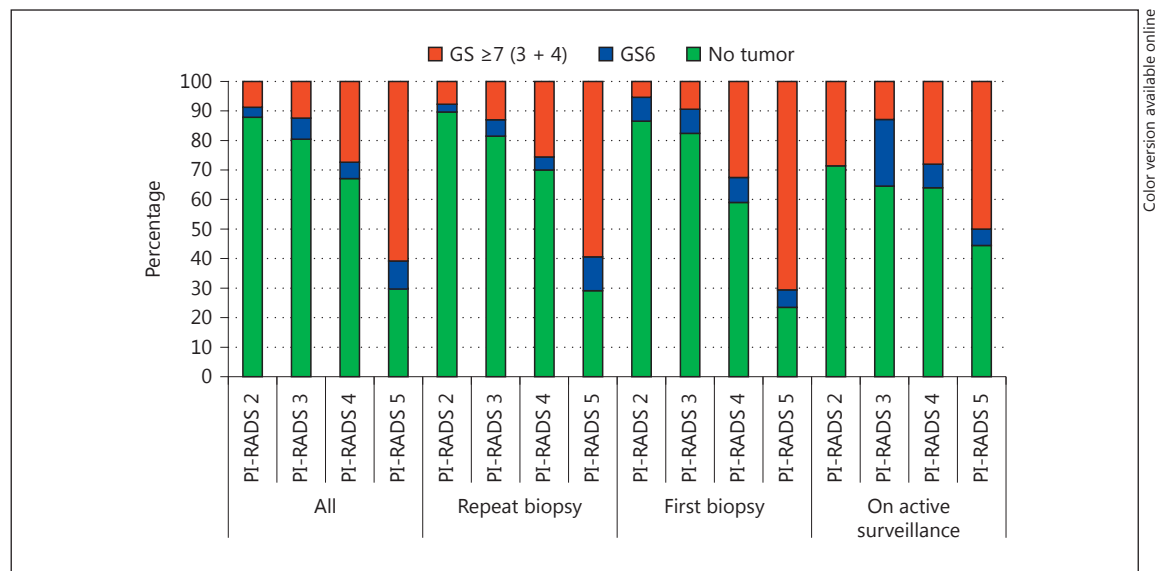


Fig. 1. Detection rate and distribution of GS in lesions detected in mpMRI compared to the biopsy result in targeted MRI/ultrasound-fusPbx in all patients and in subgroup analysis. All patients ($n = 625$; lesions $n = 1,162$): PI-RADS 2: (25/206 [12%]; GS ≥ 7 : $n = 18$ [9%]), PI-RADS 3 (88/450 [20%]; GS ≥ 7 : $n = 56$ [12%]), PI-RADS 4 (118/358 [33%]; GS ≥ 7 : $n = 98$ [27%]), and PI-RADS 5 (104/148 [70%]; GS ≥ 7 : $n = 90$ [61%]). Patients undergoing repeat biopsy ($n = 445$; lesions $n = 846$): PI-RADS 2: (16/155 [10%]; GS ≥ 7 : $n = 12$ [8%]), PI-RADS 3 (64/345 [19%]; GS ≥ 7 : $n = 45$ [13%]), PI-RADS 4 (75/250 [30%]; GS ≥ 7 : $n = 64$

[26%]), and PI-RADS 5 (68/96 [71%]; GS ≥ 7 : $n = 57$ [60%]). Patients undergoing first biopsy ($n = 133$; lesions $n = 228$): PI-RADS 2: (5/37 [14%]; GS ≥ 7 : $n = 2$ [5%]), PI-RADS 3 (13/74 [18%]; GS ≥ 7 : $n = 7$ [9%]), PI-RADS 4 (34/83 [41%]; GS ≥ 7 : $n = 27$ [33%]), and PI-RADS 5 (26/34 [76%]; GS ≥ 7 : $n = 24$ [71%]). Patients on active surveillance undergoing control biopsy ($n = 47$; lesions $n = 88$): PI-RADS 2: (4/14 [29%]; GS ≥ 7 : $n = 4$ [29%]), PI-RADS 3 (11/31 [35%]; GS ≥ 7 : $n = 4$ [13%]), PI-RADS 4 (9/25 [36%]; GS ≥ 7 : $n = 7$ [28%]), and PI-RADS 5 (10/18 [56%]; GS ≥ 7 : $n = 9$ [50%]).

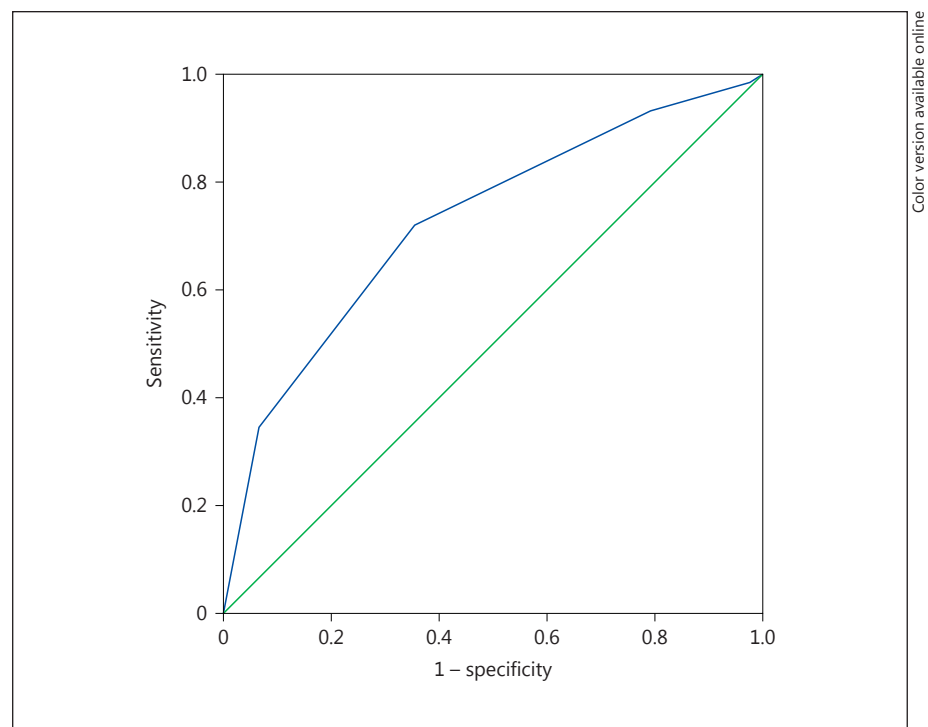


Fig. 2. ROC for the detection of clinically significant prostate cancer in lesions evaluated according to PI-RADS.

Table 5. Detection rates of PCa in MRI/ultrasound-fusion biopsy in combination to systematic biopsy with regard to the maxPI-RADS

maxPI-RADS	All PCa, n (%)	Significant PCa, n (%)
≤2 (n = 65)	21 (32)	13 (20)
3 (n = 196)	73 (37)	46 (23)
4 (n = 247)	130 (53)	102 (41)
5 (n = 117)	97 (83)	85 (73)

was detected. Twenty-three percent (13/56) of lesions classified as PI-RADS 3 with evidence of significant PCa were associated with another lesion harboring significant PCa. Similarly to lesions classified as PI-RADS 2, all of these associated lesions were classified as PI-RADS ≥4. Thirty-one percent (196/625) of patients presented maxPI-RADS 3 lesions. Twenty three of these patients presented only PI-RADS 3 lesions (23 lesions) with evidence of significant PCa. In 16 of these patients, significant PCa was detected in sysPbx as well, while 7 of these patients did not present significant PCa in sysPbx. However, 12 patients presenting only PI-RADS 3 lesions lacking evidence of significant PCa presented a significant PCa in sysPbx. In total, 14% of significant PCa (35/246) would not have been detected, if patients with only PI-RADS 3 lesions would not have undergone either targeted or sysPbx.

*Comparison of maxPI-RADS to the Biopsy Results in the Combination of fusPbx and sysPbx:
A Patient-Based Analysis*

The detection rates of all and significant PCa in comPbx according to the presented maxPI-RADS are depicted in Table 5.

In regression analysis, age, prostate specific antigen (PSA)-value, prostate volume, and a maxPI-RADS ≥4 were predictors for the detection of significant PCa in comPbx in uni- and multivariate analyses. In contrast to maxPI-RADS ≥3, maxPI-RADS ≥4 was the strongest predictor for the detection of significant PCa in comPbx (Table 6).

Discussion

In this study, we demonstrated that PI-RADS correlates with the detection of significant PCa in targeted biopsy. Furthermore, we showed that the evidence of max-

PI-RADS ≥4 is significantly associated with the detection of significant PCa in comPbx.

In both lesion- and patient-based analyses, the cancer-detection rate of significant PCa in lesions classified as PI-RADS 4 and 5 was lower than described in the current literature. Detection rates of significant PCa of up to 86 and 93% are reported for PI-RADS 4 and 5 lesions respectively [12, 13]. In another patient-based analysis (312 patients, 452 lesions), Rastinehad et al. [14] showed a detection rate of 54.4% in PI-RADS 4 and 83.6% in PI-RADS 5 for significant PCa. Additionally, in a lesion-based analysis, they showed detection rates of 36.7% in PI-RADS 4 and 81.8% in PI-RADS 5 for significant PCa.

Previous studies reported that targeted biopsy alone would miss significant PCa in 6–16% [4, 15]. Our data confirmed these results with an overall missing rate of 9% for significant PCa in fusPbx alone. Especially in patients undergoing repeat biopsy, 12% of significant PCa were missed in targeted biopsy.

Furthermore, our data demonstrated that if patients with PI-RADS 2 lesions were not investigated by comPbx, 7% of significant PCa (17/246) would be missed. Abd-Alazeez et al. [16] reported an NPV of 89–100% of mpMRI to exclude significant PCa in patients without any evidence of tumor-suspicious lesions in mpMRI. Similar data were published by Wysock et al. [17] evaluating the detection rate of 12-core biopsy in case of a negative mpMRI in 75 patients. They showed a detection rate of significant PCa of 1.3% in all and of 4% in patients with previously negative sysPbx, but no evidence of significant PCa in patients undergoing first biopsy or control-biopsy in active surveillance protocols. However, in our cohort, the detection rate of significant PCa in lesions classified as PI-RADS 2 was higher in patients on active surveillance undergoing control biopsy (29%) than that in other subgroups (3–9%). Higher detection rates of significant PCa in PI-RADS 2 lesions in patients on active surveillance may be explainable by initially higher evidence of PCa in this cohort. Almeida et al. [18] reported a correlation of visible lesions in mpMRI (defined as PI-RADS ≥4) and a risk of upstaging in patients eligible for active surveillance but undergoing radical prostatectomy. Additionally, a negative mpMRI or an mpMRI presenting PI-RADS 1 or 2 lesions should be interpreted in the context of clinical parameters (PSA-value, DRE) and the grade of suspiciousness of PCa. In these patients a sysPbx should be considered [10].

In our cohort, evidence of at least one lesion classified as PI-RADS ≥4 was the strongest independent predictor for detection of significant PCa in uni- and multivariate

Table 6. Uni- and multivariate logistic regressions analyses for determination of predictors for the detection of significant prostate cancer

Parameter	Comparison	Univariate regression analysis		Multivariate regression analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Age (median 65a)	≤ vs. > median	1.9 (1.34–2.64)	<0.005	2.09 (1.42–3.06)	<0.005
First biopsy	Yes vs. no	1.3 (0.88–1.91)	0.184		
Known PCa	Yes vs. no	1.39 (0.77–2.53)	0.279		
PSA (median 8.17 ng/mL)	≤ vs. > median	2.37 (1.70–3.29)	<0.005	2.39 (1.62–3.53)	<0.005
DRE	cT1 vs. ≥ cT2	2.01 (1.26–3.201)	0.003	1.69 (0.97–2.94)	0.064
Prostate volume (median 50 mL)	≤ vs. > median	0.22 (0.15–0.32)	<0.005	0.21 (0.14–0.31)	<0.005
maxPI-RADS ≥3	PI-RADS ≤2 vs. ≥3	2.85 (1.52–5.34)	0.001	1.34 (0.66–2.95)	0.392
maxPI-RADS ≥4	PI-RADS ≤3 vs. ≥4	3.617 (2.54–5.16)	<0.005	2.77 (1.81–4.24)	<0.005

Significant parameters are depicted in bold.

analyses. Further independent predictors were higher age, higher PSA-value, and smaller prostate volume. Furthermore, our data revealed a specificity of 65%, a low PPV of 37%, and an accuracy of 66% for the detection of significant PCa defined as GS ≥7 (3 + 4) in lesions classified as PI-RADS ≥4. However, the high NPV (89%) may underline the value of mpMRI as a triage tool for the decision to perform prostate biopsy. Nevertheless, a sensitivity of 72% indicates that mpMRI would still miss significant PCa and sysPbx should still be performed. Due to the low specificity and PPV in mpMRI, a biopsy is still needed in patients presenting with at least one lesion with a PI-RADS ≥4. Conversely, in case of a negative biopsy, but in the presence of PI-RADS 4 or 5 lesions, mpMRI and the performance of targeted biopsy should be reevaluated and a close follow-up with targeted rebiopsies should be considered [10]. For this reason, clinical parameters are still important indicators for evaluating the presence of PCa beside the mpMRI findings. Moreover, the inter-reader variability in the interpretation of mpMRI should be taken into account. In mpMRI reevaluated by experienced radiologists, a down- or upgrading of PI-RADS (v1 and v2) up to 35–45% and 13–19% was described respectively [19]. This underlines the necessity of achieving high quality and standardization in the performance and interpretation of mpMRI.

There is consensus to perform targeted biopsy in lesions classified as PI-RADS ≥3 [20]. However, the characteristics of PI-RADS 3 lesions are sparsely described. In this study, we showed in a lesion-based analysis, that 12% of detected PI-RADS 3 lesions harbored significant PCa. However, in a patient-based analysis, which evaluates patients presenting exclusively PI-RADS 3 lesions, 14% of

significant PCa would be missed if these patients would not have undergone comPbx. Liddell et al. [21] investigated 118 patients presenting 92 PI-RADS 3 lesions out of 215 lesions. They described a cancer detection rate in PI-RADS 3 lesions of only 6% (6 lesions), whereas only 2 lesions presented significant PCa. Our data underline that the presence of PI-RADS 3 lesions justifies the necessity of targeted biopsy also in combination with sysPbx due to a portion of 6% of missed significant PCa if only fusPbx were performed in patients presenting maxPI-RADS 3 lesions. However, targeting PI-RADS 2 lesions may be omitted in patients undergoing first or repeat biopsy without evidence of PCa in previous biopsy, while sysPbx should still be performed due to a high detection rate of significant PCa in 7%.

The median number of cores taken by comPbx was 19. The median number of cores in fusPbx and sysPbx was 7 and 12 respectively. This total number of cores is comparable to a saturation biopsy with 20–24 cores and above. Other study groups perform fusPbx in combination with volume-based systematic template biopsy, which results in a median number of 20–30 systematic cores, while the detection rate of all and significant PCa was comparable to our detection rates [22–24]. However, saturation and template biopsy alone still represent a methodology for a systematic but blind biopsy, unless there are no hypoechoic lesions detectable in grey-scale ultrasound. The advantage of fusPbx is the opportunity to target tumor-suspicious lesions in mpMRI. Recent data have shown that targeted fusPbx detects significantly more clinically significant PCa with a higher proportion of cores testing positive for PCa compared to template or saturation biopsy [25, 26]. Analyses of our data support

the use of mpMRI as well as the currently used reporting system (PI-RADS) for the detection of PCa. However, the diagnostic accuracy is not sufficiently high to safely omit prostate biopsies in patients with lesions classified as PI-RADS 2 and 3.

This study had several limitations. First, this study evaluated a heterogeneous population regarding demographic data or prior biopsy history, which may reduce the generalization of our results but reflect the daily practice. Second, approximately one third of our study population was evaluated by PI-RADS v2, while for the remaining two-thirds of cases PI-RADS v1 was used for evaluation of mpMRI. In this study, we did not perform a reevaluation according to PI-RADS v2 of mpMRIs investigated by PI-RADS v1 and vice versa. That may have had an influence on the detection rate due to the different weights of the performed sequences in the evaluation of lesions according to the localization in the peripheral and transitional zone. Third, targeted and sysPbx were performed subsequently by the same urologist and hence not blinded. The knowledge about the location of lesions in mpMRI could influence the operator in unintended need

placement during the sysPbx. This could result in a false high detection rate in sysPbx. Finally, because of the heterogeneous definition of clinically significant cancer, we decided to distinguish mainly between tumors with GS 6 and with GS ≥ 7 (3 + 4) for evaluation of tumor up-grading of the 2 biopsy modalities.

In conclusion, PI-RADS correlates with the tumor aggressiveness. In this study, maxPI-RADS is the strongest predictor for the detection of significant PCa in comPbx. Due to a high detection rate of additional significant PCa in sysPbx, fusPbx should still be combined with sysPbx. In case of maxPI-RADS 2, targeted biopsy may be omitted and sysPbx should be performed instead.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding.

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